

## PROCESS FOR THE PREPARATION OF CRYSTALLINE FORMS OF ORLISTAT

### Field of the Invention

5       The field of the invention relates to processes for preparing crystalline forms of orlistat, which is tetrahydrolipstatin. More particularly, it relates to processes for preparing crystalline forms of orlistat, referred to as 'Form I' and 'Form II'. The invention also relates to pharmaceutical compositions that include the crystalline Forms I and II of orlistat and use of said compositions for the treatment or prevention of obesity and  
10      hyperlipaemia.

### Background of the Invention

Orlistat is a useful pancreatic lipase-inhibiting agent and can be used for the prevention and treatment of obesity and hyperlipaemia. Chemically, it is N-formyl-L-leucine[2S-[2alpha(R\*),3 beta]]-1-[(3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester and is  
15      known from U.S. Patent No. 4,598,089.

Several processes have been reported for the purification of orlistat by chromatographic methods using toluene and ethyl acetate for example, in U.S. Patent No. 4,983,746; *Helv. Chim. Acta*. 1987, 70, 1412; *J. Org. Chem.*, 1988, 53, 1218; and 1993, 58, 7768.

20       *J. Chem. Soc. Perkin. Trans. I*, 1998, 17, 2679 reports the use of hexane and ethyl acetate for chromatographic purification of orlistat to obtain the product as an amorphous solid.

U.S. Patent No. 6,156,911; *Tetrahedron letters*, 1989, 30, 1833; *J. Org. Chem.*, 1991, 56, 4714; and *Helv. Chim. Acta*. 1987, 70, 1412 disclose a crystalline form of  
25      orlistat, obtained by recrystallization with hydrocarbons such as hexane, pentane and heptane, and characterized it by melting point and infrared spectroscopy. This crystalline form is herein after referred to as 'Form I'.

Another crystalline form of orlistat, having different X-ray diffraction pattern, is marketed by Roche as Zenical® capsules but, has not been reported in the literature. It is  
30      herein after referred to as 'Form II'.

### Summary of the Invention

In one general aspect there is provided a process for the preparation of crystalline Form II of orlistat. The process includes preparing a solution of orlistat in one or more ethers; and isolating the orlistat in the crystalline Form II from the solution thereof by the  
5 removal of the ether.

The ethers may include one or more of diethyl ether, diisopropyl ether, tert.-butyl-methyl ether, and tetrahydrofuran. In particular, the ether may be diisopropyl ether.

Removing the ether may include one or more of distillation, distillation under vacuum, evaporation, filtration, filtration under vacuum, decantation and centrifugation.

10 The process may include further drying of the product obtained.

The process may include further forming of the product so obtained into a finished dosage form.

15 The process may produce the crystalline Form II of the orlistat having the X-ray diffraction pattern of Figure 4, the infrared spectrum of Figure 5, and the differential scanning calorimetry plot of Figure 6.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically acceptable amount of Form II of orlistat; and one or more pharmaceutically acceptable carriers, excipients or diluents.

20 In another general aspect there is provided a method of treating or preventing obesity and hyperlipaemia in a warm-blooded animal, the method comprising providing a pharmaceutical composition to the warm-blooded animal that includes Form II of orlistat.

In another general aspect there is provided a process for the preparation of crystalline Form I of orlistat. The process includes obtaining a melt of orlistat; and drying the melt to get the Form I of orlistat.

25 Drying the melt may include one or more of distillation, distillation under vacuum, evaporation, and evaporation under vacuum.

In one general aspect, the melt may be cooled before drying to get a crystalline solid.

The process may include further drying of the product obtained.

The process may include further forming of the product so obtained into a finished dosage form.

The process may produce the crystalline Form I of the orlistat having the X-ray diffraction pattern of Figure 1, the infrared spectrum of Figure 2, and the differential scanning calorimetry plot of Figure 3.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically acceptable amount of Form I of orlistat; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect there is provided a method of treating or preventing obesity and hyperlipaemia in a warm-blooded animal, the method comprising providing a pharmaceutical composition to the warm-blooded animal that includes Form I of orlistat.

The details of one or more embodiments are set forth in the description below. Other features and aspects of the disclosure will be apparent from the description and claims.

#### Description of the Drawings

Figure 1 is X-ray powder diffraction (XRD) pattern of Form I of orlistat.

Figure 2 is an infrared spectrum of Form I of orlistat.

Figure 3 is differential scanning calorimetry (DSC) plot of Form I of orlistat.

Figure 4 is X-ray powder diffraction (XRD) pattern of Form II of orlistat.

Figure 5 is an infrared spectrum of Form II of orlistat.

Figure 6 is differential scanning calorimetry (DSC) plot of Form II of orlistat.

#### Detailed Description of the Invention

The inventors have developed a process for the preparation of crystalline Form II of orlistat, by preparing a solution of orlistat in one or more ethers; and isolating the crystalline Form II from the solution thereof by the removal of the ether. The inventors also have developed pharmaceutical composition that contain Form II of the orlistat, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

In general, the solution of orlistat may be obtained by dissolving any of the various forms known in the art including Form I, amorphous or waxy form of orlistat in suitable

ether. Alternatively, such a solution may be obtained directly from a reaction in which orlistat is formed. The ether containing orlistat may be heated to obtain a solution.

The ether may be removed from the solution by a technique which includes, for example, distillation, distillation under vacuum, evaporation, filtration, filtration under 5 vacuum, decantation, and centrifugation.

In another general aspect the solution may be cooled before removal of the ether to obtain better yields of the Form II of orlistat.

Suitable ethers include diethyl ether, diisopropyl ether, tert.-butyl-methyl ether, and tetrahydrofuran. Mixtures of all of these ethers are also contemplated.

10 In general, the amount of ether should be sufficient to dissolve the orlistat to get a solution. In particular, the volume of diisopropyl ether to dissolve orlistat may be from about 2 to 10 times the weight of orlistat.

15 The product obtained may be further or additionally dried to obtain the desired moisture values. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

Orlistat may be prepared using the reactions and techniques known in the art including those described in U.S. Patent Nos. 4,598,089; 4,983,746; 6,156,911; 5,412,110; 2002110873; *Helv. Chim. Acta*. 1987, 70, 1412; *J. Org. Chem.*, 1988, 53, 1218; 1993, 58, 7768; 1991, 56, 4714; *J. Chem. Soc. Perkin. Trans. I*, 1998, 17, 2679; *Tetrahedron letters*, 20 1989, 30, 1833; and *Chem. Commun.* 1999, 17, 1743.

The inventors have also developed a process for the preparation of crystalline Form I of orlistat. The process involves obtaining a melt of orlistat and drying the melt to get the Form I of orlistat.

25 In general, the melt of orlistat may be obtained by heating any of the various forms known in the art including Form II, amorphous or waxy form of orlistat. It may be heated at a temperature from about 25°C to about 80°C, or at a temperature from about 30°C to about 60°C. In particular, it may be heated at a temperature from about 40°C to about 50°C. Alternatively, such a melt may also be obtained by dissolving orlistat in a suitable solvent and removing the solvent by any of the conventional techniques including, for 30 example distillation, distillation under vacuum and evaporation.

The melted orlistat may be dried under reduced pressure to get the Form I of orlistat. In general, the melt may be cooled before drying to get a good crystalline solid.

The resulting crystalline Form II and Form I of orlistat may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these 5 cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

The compositions include dosage forms suitable for oral, buccal, rectal, and parenteral (including subcutaneous, intramuscular, and ophthalmic) administration. The oral dosage forms may include solid dosage forms, like powder, tablets, capsules, 10 suppositories, sachets, troches and lozenges as well as liquid suspensions, emulsions, pastes and elixirs. Parenteral dosage forms may include intravenous infusions, sterile solutions for intramuscular, subcutaneous or intravenous administration, dry powders to be reconstituted with sterile water for parenteral administration, and the like.

The orlistat of crystalline Form II and Form I can be administered for the treatment 15 and prevention of obesity and hyperlaemia, in a warm-blooded animal.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The present invention is further illustrated by the following examples which are provided to be exemplary of the inventions and is not intended to limit the scope of the 20 invention.

Example 1: Preparation of orlistat Form II

Orlistat Form I (2.0 g) was dissolved in diisopropyl ether (10.0 ml) and stirred at room temperature to get a clear solution. The reaction mixture was cooled to 0 to -5°C and the product was precipitated slowly with stirring. The product was filtered and washed with 25 diisopropyl ether. It was then dried at room temperature under vacuum to obtain white crystals of orlistat.

Yield: 1.7 g

XRD, IR spectra and DSC spectra were similar to those shown in Figure 4, 5 and 6, respectively.

Example 2: Preparation of orlistat Form I

2.0 g of orlistat form II was taken and the temperature was raised to 42°C using a water bath to form a melted syrup. The syrupy material was dried under reduced pressure to obtain white crystalline orlistat.

5 XRD, IR spectra and DSC spectra were similar to those shown in Figure 1, 2 and 3, respectively.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.